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A Pair of Male Fraternal Twins with Contrasting Manifestations of Rh Hemolytic Disease

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The Rh-positive newborn infant of a sensitized Rh-negative mother is a candidate for Rh hemolytic disease (1). The pathogenetic agents are the maternal Rh antibodies, which, during pregancy, traverse the placental barrier and become attached to the fetal red cells. In general, as is to be expected, the severity of the manifestations are correlated with the height of the maternal Rh antibody titer (2, 3), Thus, stillbirths are common when the maternal Rh antibody titer is very high. while when the titer is low, the baby is almost always liveborn, and, as a rule, the manifestations are mild or there may be no evidence of disease at all. However, the occurrence of exceptions (4, 5), namely, high antibody titers with little or no evidence of disease in the baby, and low titers with severe manifestations, indicates that factors other than maternal Rh antibody titer play an important role, viz., certain as yet undetermined attributes of the infant may conceivably affect the severity and course of the disease.

Some light may be thrown on this question by studies on Rh hemolytic disease in twins and triplets. Unfortunately, twins occur only once among 80 to 90 births, while triplets occur only once in about 6000 to 8000 births. Therefore, the reported observations, up to now, of Rh hemolytic disease in multiple births have been relatively few in number (5, 6, 7). In the case of identical (or monovular) twins, as expected, either both are Rh positive and affected, or both are Rh negative and normal. In the case of fraternal (or binovular) twins, one may be Rh positive and erythroblastotic, while the other may be Rh negative and therefore escape the disease. When both are Rh positive, the two twins are apt to be equally severely affected, even though fraternal and of different sexes. However, we recently encountered a pair of fraternal twins of like sex in whom the manifestations of Rh hemolytic disease were strikingly different. The purpose of this paper is to describe the findings in these twins, and to discuss the implications for the pathogenesis of the disease.

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Case Report

The patients are a pair of male, Negro twins (Hospital No. 481487), who were born after a spontaneous delivery, one month before term, at the Jewish Hospital of Brooklyn, on February 8, 1961. They were the result of the mother's third pregnancy. The mother had denied ever having received any blood transfusions, and her obstetrical history was as follows.

The first pregnancy, in 1956, had terminated with a stillbirth. During the second pregnancy, in 1957, the mother, who is Rh negative, was found to be sensitized to **Rh**$_0$ factor. The average of three antibody titrations carried out during the last three weeks of the second pregnancy was as follows: saline agglutination method,

Tab. 1. Results of Rh Antibody Titrations on the Serums of the Mother and Twins

Time of test		Titer of Rh antibodies by method of			Ficinated cells
		Agglutination	Albumin-plasma conglutination	Antiglobulin	
During 2nd pregnancy (1957)	8th month a)	1½	24	14	124
	b)	2	52	80	290
	9th month	1	16	24	144
	Average of above 3 titers	1½	31	39	186
	Postpartum	0	20	22	224
During 3rd pregnancy (1960)	2nd month	0	4	4	40
	3rd month	0	1	5	64
	4th month a)	0	6	5	56
	b)	0	0	6	56
	Average of above 4 titers	0	3	5	54
	5th month	0	1	16	60
	6th month	0	8	12	40
	7th month	0	8	22	84
	8th month	1	12	56	72
	Average of above 4 titers	0	7	26	64
	Twin A	0	0	0	24
	Twin B	0	0	1	27

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1½ units; albumin-plasma conglutination method, 31 units; antiglobulin method, 39 units; ficinated cell technique, 186 units (cf. table 1). The mother's blood groups were group A_1, type rh; the father's, group O, type Rh_0; while the infant's were group A_1, type Rh_0. Despite the fact that this baby was Rh positive, and that the direct antiglobulin test was positive (12½ percent of maximal coating), the cord icterus index proved to be only 7 units, and the hemoglobin concentration was 15 grams percent. On the second day of life, the baby was still not jaundiced, and the icterus index was only 12 units, but the hemoglobin concentration had dropped to 13.7 grams percent. Thereafter, this baby developed a mild hemolytic anemia from which he recovered completely, following two small transfusions of sedimented red cells.

During the third pregnancy, which gave rise to the twins, who are the subject of this report, antibody titrations were carried out, starting with the first trimester. As can be seen from table 1, the results suggest that there was mild rise in antibody titer during the fourth or fifth month of pregnancy. As has already been pointed out, the father is type Rh_0, and from the available serologic and genetic evidence, it is not possible to ascertain whether he is homozygous or heterozygous for the **Rh_0** factor. If the evidence that there had been a rise in antibody titer could be taken at face value, this would exclude the possibility that the fetus in utero was Rh negative. In fact, when the twins were born they both proved to be type Rh_0.

The birth weights of the twins were: twin A, 5 lbs, 6½ oz.; twin B, 4 lbs., 8½ oz. Both twins were group A_1, type Rh_0, but twin A was type N while twin B is type MN, proving that the twins were binovular, although both males. As will be shown, the clinical course of the twins also proved to be dissimilar, when their progress was followed during the neonatal period.

In fact, already at birth, the clinical findings on the twins were different, despite the similarity of the serologic findings. As already mentioned, the twins were both type Rh_0, and as expected, the quantitative direct and antiglobulin test was positive in both twins (twin A, 33 percent of maximal coating; twin B, 25 percent of maximal coating), and the free Rh antibody titers in the cord serums of both twins did not differ significantly (cf. table 1). In twin A, the cord icterus index was 15 units, and the total bilirubin concentration 3.25 mgs. percent; in twin B, the cord icterus index was 15 units, and the total bilirubin 3.45 mgs. percent. However, while in twin B the direct bilirubin concentration was low, 0.65 mgs. percent, which is the usual finding, in twin A, the direct bilirubin concentration in the cord was 1.85 mgs. percent.

Twin B

During the next few days, twin B presented the typical course of a mildly to moderately affected erythroblastotic baby. While the cord icterus index and bilirubin concentration had been at the upper limits of normal, the baby soon developed a progressively increasing hyperbilirubinemia. Within a few hours after birth, minimal jaundice could already be detected, and by the next morning, the baby

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was definitely jaundiced. A blood count taken on the day of birth showed a hemoglobin concentration of only 10.8 grams percent; red blood cell count, 3.5 million/cu.mm.; white blood cell count, 19,000/cu.mm.; differential: polys 51 (no band forms), lymphs 46, eos. 1, baso 2. The platelets appeared normal on smear, but there was marked anisocytosis of the red cells with frequent macrocytes and moderate polychromasia; in addition, there were 8 nucleated red cells per one hundred white cells. By the morning of the second day when the jaundice had become manifest, the serum icterus index had risen to 96 units and the serum bilirubin concentration to 15.9 mgs. percent (almost entirely indirect reacting). Therefore, the baby was treated by exchange transfusion, which was carried out by the radial-artery/saphenous-vein technique. For the transfusion, 2 units of two day old group A, type rh bank blood were used, from which part of the plasma had been removed, sufficient to produce an hematocrit of approximately 0.50. The exchange transfusion was well tolerated and the baby was returned to the nursery in excellent condition. As can be seen from table 2, the icterus index of the first sample drawn at transfusion was 108 units, while that of the last sample was only 24 units.

Following the exchange transfusion, the baby's jaundice soon faded and the subsequent course was essentially uneventful. Blood count taken on the day after the exchange showed a hemoglobin concentration of 16 grams percent; red blood cell count, 5.38 million; white blood cell count, 18,450; differential: polys 94 (no bands), lymphs, 5, eos 1. Nucleated red blood cells were no longer present on the smear, but there were 5 percent reticulocytes. On the fourth day of life, the icterus index was only 80 units, and the total serum bilirubin concentration was 12.6 mgs. percent, of which 4 mgs. percent was direct. This was the highest concentration of direct reacting bilirubin that this twin had during his first month of life. Thereafter, the jaundice rapidly faded, and this was associated with a drop of the serum bilirubin concentration. However, the baby was kept at the hospital so that both twins could be discharged at the same time. When the baby was discharged at the age of one month, he was apparently normal, the icterus index at this time being only 3 units and the serum bilirubin concentration 0.5 mgs. percent.

Twin A

As has already been mentioned, the course in twin A was strikingly different. The initial blood count was more nearly normal, as follows: hemoglobin concentration, 12.7 grams percent; red blood cell count, 4.17 million; white blood cell count, 17,000; differential; polys 48 (no bands), lymphs 51, basos 1. The platelets were normal on smear, and the red cells showed only slight anisocytosis and rare polychromasia. There were no nucleated red blood cells on smear, but there were 8 percent reticulocytes. On the second day of life, twin A showed no evidence of jaundice, and the blood count had not changed appreciably. The icterus index was only 40 units, and the total serum bilirubin concentration was 8.1 mgs. percent. However, of the total serum bilirubin, 6.2 mgs. percent were direct reacting, in con-

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trast to the finding on twin B, and in contrast to the usual situation. On the third day of life, there was no change, giving one the impression that the serum bilirubin concentration had reached or even passed its peak, because the icterus index was again 40 units and the total bilirubin concentration was only 6.4 mgs. percent. During the next few days, however, the baby became deeply jaundiced and there was an associated rise in the serum bilirubin concentration. Treatment by exchange transfusion was withheld because, of the total bilirubin, only a small fraction was indirect reacting, and direct reacting bilirubin is considered to be innocuous in the pathogenesis of kernicterus. The peak of the jaundice occurred on the eighth day of life, at which time the icterus index had reached 144 units and the total serum bilirubin concentration was 27.0 mgs. percent, of which 23.3 mgs. percent was direct reacting. Thereafter, the jaundice gradually diminished. When the baby was discharged on the twenty-eighth day of life, he was still mildly jaundiced; the icterus index was 18 units and the serum bilirubin concentration was 8.1 mgs. percent, all direct.

The intensity of the jaundice in twin A was such that despite the natural pigmentation of his skin, the baby presented a striking appearance. The skin assumed a somewhat greenish hue, but, despite this, the clinical behavior of the baby appeared satisfactory. At no time did the infant exhibit any evidence of brain damage. There was no hyperpyrexia, no opisthotonus, no high pitched cry, and there was a good Moro reflex. The baby did, however, develop a mild anemia. When he was twelve days old, the hemoglobin concentration was only 8.1 grams percent; red blood cell count, 2.70 million; white blood cell count, 10,960; differential: polys 54, lymphs 40, monos 4, eos 2; there were no nucleated red blood cells, but there were 3.5 percent reticulocytes on smear. The baby was therefore given a small transfusion of packed cells, but received no other treatment.

The findings indicated that twin A had the so-called « inspissated bile » syndrome. In fact, on the sixth day of life, when the jaundice had become marked, examination of the stool specimen showed it to be lemon color and virtually free from bile. A urine sample collected at the same time had a deep reddish-brown hue, and by the acetone method, the icterus index of the urine was shown to be 24 units, while the total bilirubin concentration was 2.1 mgs. percent, all direct. In contrast, a stool specimen obtained from twin B at the same time proved to be a normal brown color, containing bile, while the urine was pale and had no bile in it.

Because of the evidence indicating the presence of an obstructive jaundice, the possibility was considered that twin A might have some congenital anomaly of the bile ducts. However, the fact that the jaundice gradually cleared after the eighth day of life ruled this out.

Another diagnosis that was considered was hepatitis, but this diagnosis seems improbable because the twin B was not affected. Blood chemical studies were done on twin A on the seventh day of life with the following results: alkaline phosphatase, 8.7 Bodansky units; cephalin flocculation, 0.3 units; thymol turbidity, 15 units;

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SGP transaminase, 78 units (control 40 units). The elevated alkaline phosphatase, thymol turbidity and SGP transaminase are evidence of liver damage.

As has been pointed out, after the eighth day of life, the jaundice began to subside, but improvement was much slower than in twin B (cf. table 2). In fact, on the tenth day of life, at which time twin B was no longer jaundiced, twin A was still very deeply jaundiced. Thereafter, the improvement was steady but slow, and on the twenty eighth day of life, when the twins were discharged, twin A was still noticeably jaundiced.

Tab. 2. Results of Icterus Index and Bilirubin Determinations on the Blood of the Twins

Day of life	Twin A			Twin B		
	Icterus index* (units)	Serum bilirubin (mgs./100 c.c.)		Icterus index (units)	Serum bilirubin (mgs./100 c.c)	
		Direct	Total		Direct	Total
Cord. blood.	15	1.8	3.2	18	0.6	3.45
2	40	6.2	8.1	98	1.5	15.9
				pre exch. 108	1.8	16.4
				post exch. 24	N.D.	N.D.
3	40	5.7	6.4	N.D.	2.5	11.5
4	84	8.8	9.2	80	4.0	12.6
6	96	16.9	22.5	48	2.2	6.8
8	144	23.3	27.0	30	N.D.	N.D.
10	108	21.4	N.D.	N.D.	0.4	2.9
13	60	12.6	17.5			
16	60	12.5	16.0			
21	40	10.7	14.0			
28	18	8.1	8.1	3	0.15	0.5
135	2	0.1	0.2			

*Acetone method.
N.D. = not done

At the time of discharge, twin A weighed 5 pounds, 15 ounces, having gained only 8½ ounces above birth weight. Twin B, in contrast, weighed 6 pounds 7 ounces and had gained 1 pound, 14 ounces over his birth weight. Hematologically, there was not much difference between the twins, since twin A had a hemoglobin concentration of 8.1 grams percent, red blood cell count 2.56 million; and twin B had a hemoglobin concentration of 7.8 grams percent, red blood cell count 2.8 million.

Both twins were seen again when they were 135 days of age. At this time they both were apparently well; twin A weighed 9 pounds, 6 ounces, while twin B weighed

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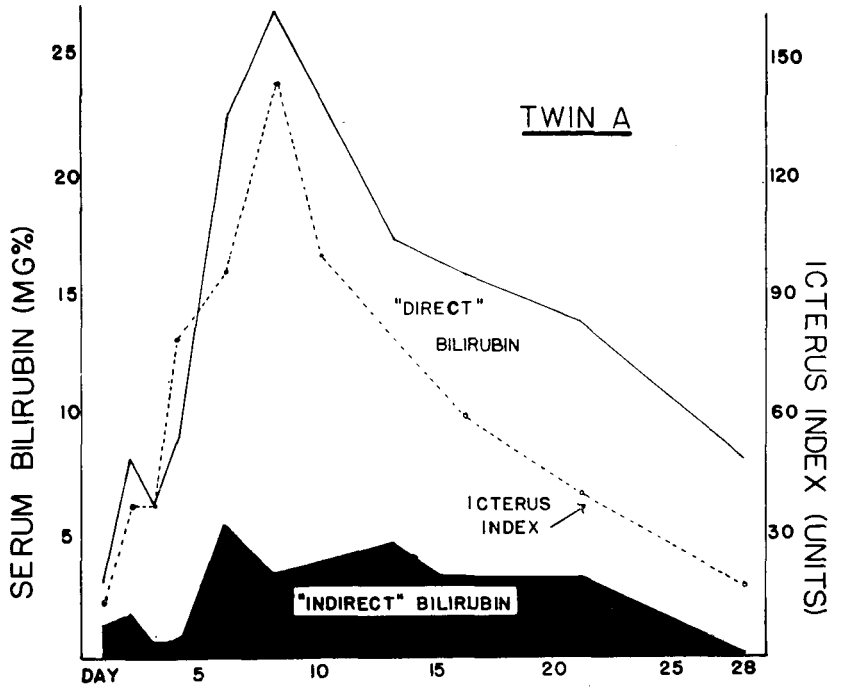

Fig. 1. Results of Serial Icterus Index and Bilirubin Determinations on Twin A. Broken line denotes icterus index; solid line denotes total bilirubin; black area denotes indirect reacting bilirubin; white area denotes direct reacting bilirubin

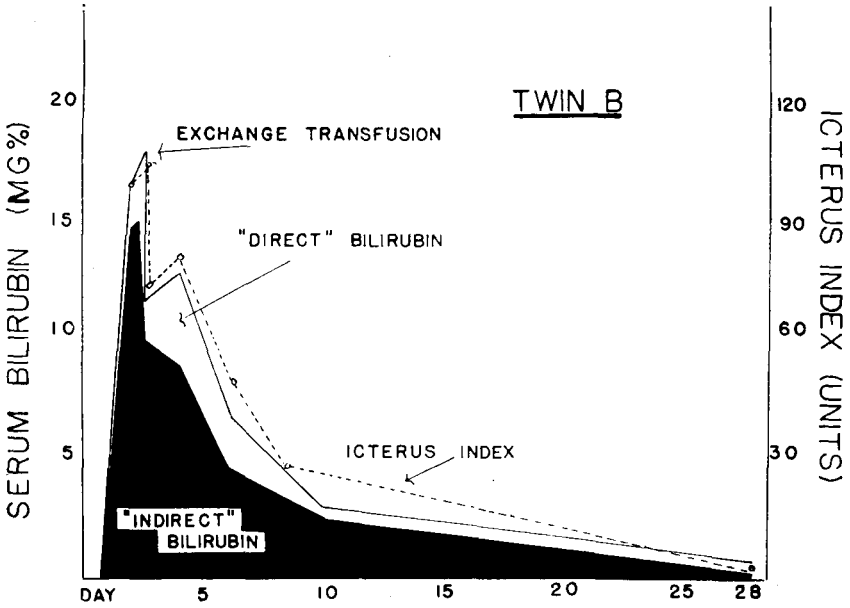

Fig. 2. Results of Serial Icterus Index and Bilirubin Determinations on Twin B. Broken line denotes icterus index; solid line denotes total bilirubin; black area denotes indirect reacting bilirubin; white area denotes direct reacting bilirubin

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9 pounds, 13 ounces. Neither showed any evidence of jaundice and were developing normally, mentally as well as physically.

The contrast in the behavior of twin A and twin B is demonstrated most strikingly by plotting the serum bilirubin concentrations and icterus index values (cf. figs. 1 and 2). The correlation between icterus index values and the serum bilirubin concentration is closer in the case of twin B than in twin A. In our experience, the icterus index values, as determined by the acetone method, are generally five to seven times the serum bilirubin concentrarion. However, this ratio did not hold in the case of twin A, especially towards the end of his stay in the hospital when the icterus index determinations fell far short of the expected walues. For example, on the twenty-eighth day of life, twin A's serum bilirubin was 8.1 mgs. percent, but the icterus index was only 18 units. It was then found that, if when diluting the serum to read the icterus index value, water instead of acetone was used, the test gave the expected value of 48 units. Ordinarily, the same reading is obtained whether acetone or water is used as the diluent. The purpose of the acetone is to precipitate the proteins, and its use makes possible a reliable reading even when testing hemolyzed samples. However, in the case of twin A, almost all of whose serum bilirubin was of the direct reacting type, the acetone evidently precipitated not only the protein, but also some of the bilirubin, which accounted for the low icterus index values obtained.

It is of importance to emphasize that already at birth bilirubin determinations on twin A had showed him to be demonstrably different from normal babies, as from twin B, in that the bulk of his bilirubin was direct reacting. Whatever the nature of the peculiarity responsible for this phenomenon, it was evidently already present before birth. The so-called inspissated bile syndrome has always been regarded as a complication of untreated erythroblastosis fetalis. Our observations, however, suggest that the appearance of the syndrome depends upon the presence of some peculiarity of the baby already present before birth. Moreover, by adequate bilirubin tests on cord serum, it may prove possible in the future to predict at birth the future development of this rare syndrome. It still remains to be determined whether or not early exchange transfusion can affect the course of the process.

Comment

The contrast in the behavior of twin A and twin B, despite the virtually identical serological evidence of disease, is a striking demonstration that antibody titers and other serological findings are not the sole factors determining the severity of the manifestations. There are reasons to believe that constitutional factors in the affected baby also play an important role. Therefore, while in identical twins one may reasonably expect the manifestations in both twins to be similar, in fraternal twins, the possibility exists that the manifestations could be quite different, as in the case of the twins described in this report. It is fortunate that the results of the M-N test

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proved that the twins were not identical; otherwise, the difference in their behavior would have been even more puzzling.

A promising field of investigation would be to search for constitutional factors in the baby which can affect the course of the disease. If one can discover why some Rh-positive babies show no clinical evidence of disease despite a very high Rh antibody titer in both the mother and baby, and despite maximal coating of the baby's red cells by Rh antibodies, this might lead to new methods of treating the disease. In fact, it is conceivable that the day may come when erythrobastosis will be treated by biochemical means rather than exchange transfusion. It is unfortunate that, to date, there is no clue as to the mechanism whereby certain of these babies escape the deleterious effects of incompatible maternal antibodies.

Summary

A pair of male, Negro, fraternal twins are described, both of whom were affected with Rh hemolytic disease. In one twin, the manifestations were typical; jaundice appeared early, exchange transfusion was carried out, and this was followed by prompt and complete recovery. In the second twin, who was treated expectantly, jaundice appeared later and followed the protracted course of the so-called «inspissated bile» syndrome, i. e., the stools were acholic, there was bile in the urine, and most of the serum bilirubin was of the direct reacting type. Of interest was the finding that the occurrence of the syndrome was presaged by the presence of excessive amounts of direct reacting bilirubin in the cord serum. This twin also recovered completely, but convalescence was more prolonged.

The observations on these twins provide further evidence that the constitution of the baby, in addition to the maternal Rh antibody titer determine the nature and severity of the manifestations in an erythroblastotic baby.

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RIASSUNTO

Si riferisce su di una coppia di gemelli DZ negri di sesso maschile, ambedue affetti da malattia da situazione Rh. In un gemello il decorso fu tipico: l'itterizia apparve presto, fu effettuata una exanguinotrasfusione che fu seguita da guarigione pronta e completa. Nel co-gemello, che fu trattato in maniera aspettante, l'itterizia comparve più tardi, dopo il decorso prolungato della cosiddetta sindrome della bile condensata, caratterizzata da feci acoliche, bile nell'urina e da bilirubina serica per lo più del tipo diretto. Interessante il reperto che il verificarsi della sindrome era presagito dalla eccessiva quantità di bilirubina diretto nel siero del cordone ombelicale. Anche questo gemello si ristabilì completamente, ma la convalescenza durò più a lungo.

Le osservazioni compiute su questi gemelli forniscono ulteriori prove del fatto che la costituzione del bambino contribuisce anch'essa, oltre al titolo anticorpale Rh materno, a determinare la natura e la gravità della manifestazione nel bambino eritroblastotico.

RÉSUMÉ

L'on rapporte sur un couple de jumeaux DZ nègres de sexe masculin, tous les deux atteints de la maladie hémolytique par Rh. Chez un des jumeaux les manifestations furent typiques: l'ictère apparut tôt et, après avoir administré une transfusion d'echange, la guérison fut prompte et complète. Chez le partenaire, qui fut traité de façon expectante, l'ictère apparut plus tard, après le décours prolongé du syndrome appelé « de la bile inspissée », c'est-à-dire les selles étaient acholiques, il y avait de la bile dans l'urine et la majorité de la bilirubine du sérum était du type directement réagissant. Il a été intéressant de constater que la manifestation du syndrome fut présagée par la présence d'une quantité excessive de bilirubine directement réagissante dans le sérum du cordon ombilical. Ce jumeau aussi guérit complètement, mais sa convalescence fut plus prolongée.

Les observations accomplies sur ces jumeaux nous fournissent une preuve de plus que la constitution de l'enfant, outre le titre anticorpal Rh de la mère, determine la nature et la gravité des manifestations chez l'enfant erythroblastotique.

ZUSAMMENFASSUNG

Beschreibung eines Paares männlicher, brüderlicher Neger Zwillinge, die beide mit Rh hämolytischer Krankheit behaftet waren. Bei einem der Zwillinge waren die Erscheinungen typisch: Ikterus trat frühzeitig auf, die durchgeführte Austauschtransfusion hatte rasche, vollständige Genesung zur Folge. Beim zweiten Zwillinge, der zuwartend behandelt wurde, trat die Gelbsucht später auf, und wurde vom protrahierten Verlauf des sogenannten « verdickte Galle » Syndroms gefolgt, das heisst, der Stuhl war acholisch, Anwesenheit von Gallenfarbstoff im Urin, und das Meiste des Serum Bilirubins war vom direct reagierenden Typus. Interessant war der Befund, dass das Auftreten des Syndroms von der Anwesenheit übermässiger Mengen von direct reagierendem Bilirubin im Nabelschnur Serum vorausgesagt werden konnte. Auch dieser Zwilling genas vollständig, aber seine Rekonvaleszenz war mehr verschleppt.

Die Beobachtungen an diesen Zwillingen liefern den weiteren Beweis, dass die Konstitution des Säuglings, ausser dem mütterlichen Rh Antikörper Titer, die Natur und Schwere der Manifestationen in einem erythroblastotischen Kinde bestimmt.

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Rh-Hr Nomenclature

Despite the great importance of the field of blood grouping, no action has been taken regarding the suggestion to settle the vital problem of Rh-Hr nomenclature now, without further delay. The argument to let time settle the problem is fallacious because time has never settled any scientific problem unassisted, but merely allows false ideas, misconceptions and bad nomenclature to become more firmly entrenched.

Publications continue to appear which indicate the wide popularity of the C-D-E notations, despite the fact that standard medical dictionaries give only the original, and correct Rh-Hr nomenclature. This popularity is based first on the supposed simplicity of the symbols, and secondly on the initially seeming success of Fisher's "predictions". The first reason can be immediately dismissed, because scientists are concerned only with what is correct, rather than with what is simple. This communication will therefore be confined to a comparison between the predictions made under my own theory and those made under Fisher's theory, and their bearing on the nomenclature problem.

The distinction which I have repeatedly emphasized between agglutinogens (intrinsic attributes of the red blood cells), and blood factors (extrinsic attributes of the agglutinogens of the red blood cells) is the basis for the Rh-Hr teminology. This concept led me to the prediction that corresponding to each agglutinogen an infinite number of different specific antibodies would be found, so that each agglutinogen is characterized by not merely a single blood factor, but by a specific *set* of blood factors or serological specificities. This prediction has been and is being fulfilled by the discovery of an ever increasing number of Rh-Hr blood factors, totalling more than 20 by the latest count, including such blood factors as **Rh^{A}**, **Rh^{B}**, **Rh^{C}**, **Rh^{D}**, and **hr^{S}** This concept serves also as a stimulus for further work and study, with the assurance that the number of Rh-Hr blood factors found will be limited only by one's industry and ingenuity in searching for and finding antisera of new specificities.

In contrast, the simple Fisher scheme is limited to only 6 blood factors, C-c, D-d, and E-e. The seeming success of Fisher's prediction of little d and little e would appear to refute my own concept of an infinite number of blood factors corresponding to each agglutinogen, because that concept implies that the specificities of the blood factors still to be found are largely unpredictable. As a matter of fact, it turns out that Fisher's predictions are entirely wrong. Firstly, anti-little d has never been found, despite the claims of certain impressionable and eager investigators. (The fact that these claims have been proved to be wrong has not prevented certain authors from exploiting the supposed discovery of little d as proof of the Fisher synthesis). I need not belabor further here the false claims regarding little d, and the paradoxes and serious errors to which these have led. Unfortunately, these false facts are still being taught to impressionable students who will be doomed to carry this misinformation and these misconceptions with them for the remainder of their professional careers. Also the prediction of little e has turned out to be wrong, even

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though this does not appear to be realized by most workers in the field. M. Shapiro's work has shown that thore is not merely a single factor e **(hr″)** contrasing with E **(rh″)**, but at least two, designated **hr″** and **hr^s**. Moreover, the contrast between E and e is apparent rather than real, since it is merely a statistical effect. Thus, if we imagine a human isolate with a very high frequency of the genes $\overline{\overline{R}}^o$ and/or $\overline{\overline{R}}^w$ the contrast between E and e would largely disappear, and their relationship would parallel that of genes *A* and *B*, rather than of genes *M* and *N*. Finally, as I have repeatedly pointed out, there are not merely 6 Rh-Hr blood factors, since already at least 20 are known, and attempts to fit these within the narrow confines of CDE have failed, and led to contradictions and errors.

Therefore, scientific journals should permit the use only of the original Rh-Hr nomenclature, in conformity with the best dictionary usage, and the CDE symbols should be discarded completely and permanently. This will conform with the findings and recommendations of the American Medical Association's Committee on Medicolegal Problems, whose reports published in 1956 and 1957 have by now withstood the test of time.

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